The Value of Risk Reduction in CNS Drug Development: Use of Expected Net Present Value (eNPV) as a Model

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INTRODUCTION

Recent data suggests that the probability of success in a phase II clinical trial has the largest influence on R & D productivity of any of the features explored across all phases of discovery and clinical development[1]. However, failure rates in phase II are quite high, particularly in CNS. For phase II and III CNS clinical trials (e.g., major depressive disorder) when a drug ultimately demonstrated to be effective is compared vs. placebo the probability of a statistically significant difference is approximately 50%[2], much lower than the 80% to 90% success rate expected from the statistical powering of these studies. Several methods have been proposed to reduce the risk of CNS trial failure[3]. These methods include review of recorded assessments, novel clinical trial designs, Central Ratings in lieu of site ratings and innovative statistical methods, to name a few. However, to our knowledge, quantitative modeling has not been used to assess how much value risk reduction methods may add to the R&D process.

METHODS

The economic impact of applying risk reduction methods to CNS clinical trials is estimated using expected Net Present Value (eNPV). eNPV calculates all cash flow expected, adjusted for time and the probability of success.

- For example, a product that costs $20 to produce with a 50% chance of generating $120 of revenue immediately has an eNPV of $50 (($120 - $20)*50%).
- If there is any delay in the revenue, an annual discount rate must be applied to cover the cost of capital.

eNPV is commonly used in drug development (and other industries) where one must estimate the probability of success at each phase of development, as well as future revenues.

At time of launch the NPV of a drug that will deliver $1 billion peak annual sales is estimated under the conditions to the right[1,4,5]:

Lifespan of Drug Post-Launch (in years)	18
Patent Life After Launch (in years)	10
Peak Sales ($)	$1,000,000,000
Duration of Peak Sales (in years)	6
Time to Peak Sales (in years)	4
Sales Prior to Reaching Peak($)	
Year 1	0
Year 2	$250,000,000
Year 3	$500,000,000
Year 4	$750,000,000
Sales Post-Patent Expiry ($):	
Years 11 -16	$100,000,000
Years 17 – 18	$50,000,000
Cost of Goods Sold (COGS; %)	15
Sales and Marketing Expenses (MKTG; %)*	20
Discount Rate (%)	12
Cost of Phase IV Commitment in Years 2-3 (per year) ($)**	$2,000,000
Marginal Tax Rate (MTR; %)	25

*Calculated as 20% of total expected sales over 18 years ($1,640,000); spent at a variable rate (% of total sales & marketing expenditures by year in years 1 - 11): 5, 10, 20, 20, 15, 10, 10, 5, 2, 1, 1

**Calculated as $10,000 per patient X 200 patients per year X 2 years

NPV is calculated as:

$$NPV_{(i,N)} = \sum_{t=1}^{N} \frac{R_t}{(1+i)^t} \quad \text{where} \quad R_t = S_t - (COGS_t + PIV_t + MKTG_t)$$

and

t = time period of cash flow (i.e., year of sale) — i = discount rate

R_t = net cash flow — S_t = sales at time period

$COGS_t$ = cost of goods sold at time period — PIV_t = cost of phase IV commitment at time period

$MKTG_t$ = sales and marketing expenses at time period

NPV is then adjusted for the Marginal Tax Rate (MTR) such that:

$$NPV_{(after\ tax)} = NPV * (1 - MTR)$$

Next, the risk adjusted value of the drug at the start of phase IIa is calculated as:

$$NPV_{(risk\ adjusted)} = NPV_{(after\ tax)} * P_{(success)}$$

Using the following probabilities of success for standard risk:

	Probability of Success (%)	Phase Duration (in months)	Cost
Phase IIa	**50**		**$6,000,000**
Phase IIb†	91	**30**	$30,000,000
Phase III	97	40	$96,000,000
Registration	96	36	
Cumulative	43	106	$136,000,000

† Clinical trial costs shown are for successful trials at each phase. Whereas successes in phase 2b and phase 3 are assumed to cost $30 million and $96 million respectively, a failure in phase IIb or phase III is assumed to cost $12 million and $48 million respectively. A phase IIa failure is assumed to cost the same as a phase IIa success.

Finally, eNPV at the start of phase IIa subtracts from the risk adjusted value of the drug, the time-discounted cost of bringing the drug from phase IIa to launch using the phase durations and time-adjusted costs above.

$$eNPV = \left(\frac{NPV_{(risk\ adjusted)}}{(1+i)^n}\right) - CCT(risk\ adjusted)$$

n = # of years from study start to registration

CCT (risk adjusted)= attrition risk-adjusted, time-discounted cost of running clinical trials

Lastly, to assess the impact of applying risk reduction, eNPV is calculated under the following 6 conditions:

All models are estimated holding the probability of success in other stages of development constant to isolate the impact of risk reduction in the phase manipulated.

Phase IIa
- 50% Probability of Success (i.e., standard risk)
- 51% Probability of Success (i.e., a 1% reduction in failure rate)
- 70% Probability of Success (i.e., a 20% reduction in failure rate)

Phase III
- 81% Probability of Success (i.e., standard risk)
- 82% Probability of Success (i.e., a 1% reduction in failure rate)
- 97% Probability of Success (i.e., a 20% reduction in failure rate)

These largely CNS-specific assumptions are consistent with published findings using similar models[1].

RESULTS

The NPV of a $1 billion drug at launch, using these assumptions, is estimated to be $1.663 billion.

	Standard Risk	Risk Reduced by 1%	Risk Reduced by 20%
NPV of Drug at Launch	$1,663,001,703	$1,663,001,703	$1,663,001,703
Probability of Success after One Phase IIa Trial	50%	51%	70%
Probability of Success through Phase IIb	91%	91%	91%
Probability of Success through Phase III	97%	97%	97%
Probability of Success through Registration	98%	98%	98%
Cumulative Probability of Launch at Start of Phase IIa	43%	44%	61%
Risk-Adjusted Value (eNPV) at Start of Phase IIa	$719,286,486	$733,672,215	$1,007,001,080
Months in Phase II	30	30	30
Months in Phase III	40	40	40
Months in Registration	36	36	36
eNPV at Start of Phase IIa before cost of clinical trials	$264,327,714	$269,614,269	$370,058,800
Risk-adjusted cost of clinical trials from Phase IIa to launch*	$52,188,415	$52,188,415	$68,308,899
eNPV at Start of Phase IIa	$212,139,299	$217,425,854	$301,749,901
Risk Reduction Value Added*		**$5,286,555**	**$89,610,602**

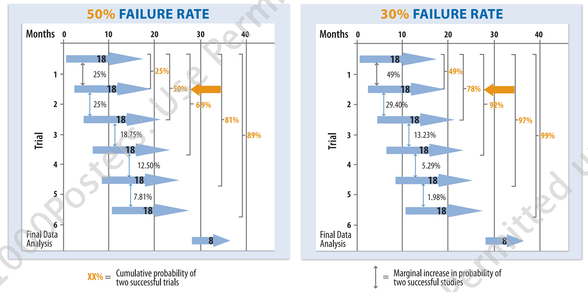
*All estimates before adjusting for the incremental cost of risk reduction methods.

In the standard risk approach, the $1.663 billion value of the drug at the time of launch is diminished to $719.286 million when multiplied by the 43% cumulative probability.

When risk reduction is assumed to increase the probability of success to 61%, the value of the drug at launch increases to $1.007 billion. After adjusting the net present value by a 12% annual discount rate the eNPV is increased by $89.611 million.

Increasing the probability of success in phase IIa by just one percentage point increased eNPV by $5.286 million after adjusting for the discount rate.

Phase III: If the failure rate is lowered from 50% to 30%, the overall probability of success in phase III, modeled here as at least two successful trials out of five, increases from 81% to 97%.



	Standard Risk	Risk Reduced by 1%	Risk Reduced by 20%
NPV of Drug at Launch	$1,663,002,000	$1,663,002,000	$1,663,002,000
Probability of Success after Five Phase III Trials	81%	82%	97%
Probability of Success through Registration	98%	98%	98%
Cumulative Probability of Launch at Start of Phase III	79%	80%	95%
Risk-Adjusted Value (eNPV) at Start of Phase III	$1,320,091,000	$1,336,388,000	$1,580,849,000
Months in Phase III	40	40	40
Months in Registration	36	36	36
eNPV at Start of Phase III before cost of clinical trials	$ 644,005,602	$651,956,288	$ 771,216,585
Risk-adjusted cost of clinical trials*	$78,710,375	$78,710,375	$85,258,679
eNPV at Start of Phase III	$565,295,227	$573,245,913	$685,957,906
Risk Reduction Value Added*		**$7,950,686**	**$120,662,679**

*All estimates before adjusting for the incremental cost of risk reduction methods.

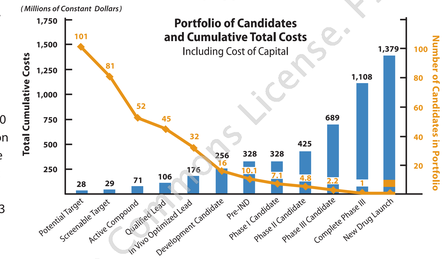
As a result of risk reduction in each phase III study, the overall probability of launching the drug rises from 79% to 95%.

The $1.663 billion value of the drug at launch is diminished to $1.320 million adjusting for the cumulative probability of 79% under standard risk.

Increasing the probability of success in phase III by 20% increases the value of the drug at launch to $1.581 million thus increasing the eNPV by $120.663 million.

A 1% improvement in phase III probability of success increased eNPV by $7.951 million.

Using standard risk, a portfolio of 101 targets (in the early phase of the discovery process) is required to yield one successful drug launch. The cumulative cost of that one drug, including the cost of failures, is $1.379 billion. The difference between the eNPV of $1.663 billion and the $1.379 billion investment is just over $284 million. The $89.230 million value added by risk reduction represents a 31% improvement. The $89.611 million value added by risk reduction in phase IIa represents a 32% improvement and the $120.663 million value added in phase III is a 43% improvement.



DISCUSSION

Quantifying the dollar value of reducing the risk of failure in phases II and III underscores the significant return on investment afforded by methods that can reduce clinical trial failure rates even slightly, not to mention their potential to advance medical science by averting false negatives that keep important new drugs from patients who need them. Serious consideration should be given, from both a financial and medical perspective, to methods for reducing attrition, especially in disease states with known high rates of failed trials, such as MDD, CIAS, AD and many other CNS disorders.

There are many limitations to this analysis. All of the assumptions about sales, patent life, success rates of trials and phases, and development times are just that – assumptions. They may be very inappropriate for a specific drug development plan. However, all are within the range of published literature, and the general approach taken here can be easily modified, for example, to fit a drug with 5 years of marketed patent life instead of 10, etc. The quantitative estimates (1%; 20%) of potential impact of employing risk reduction methods are also illustrative assumptions that are easily modified but are assumptions rather than demonstrated results. Further, these estimates do not include the incremental costs of employing risk reduction methods in clinical trials. Lastly, the simulations of phase II and III value increments assume the development of a drug which is, in fact, safe and effective and ultimately approved for commercialization. However, additional simulations can be brought to bear across portfolios of successful and unsuccessful drugs, and there is also incremental value to improved signal detection in the case of unsuccessful drugs (i.e., fail faster).

Worth considering is that many aspects of improved signal detection are not assessed here, and in these cases we attempted to err consistently on the conservative side. For example, more successful trials earlier could have several other positive impacts on NPV, such as potential first-to-market advantages in regulatory review time, first-mover advantage in marketing and sales, etc.

References: [1]Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Shacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug Discovery 2010; 9: 203-214. [2]Khin Ni A. et al. (2011). Exploratory Analyses of Efficacy Data From Major Depressive Disorder Trials Submitted to the US Food and Drug Administration in Support of New Drug Applications. Journal of Clinical Psychiatry. 72:4, 464-472. [3]Mallinckrodt CH, Tamura RN, Tanaka Y. Recent developments in improving signal detection and reducing placebo response in psychiatric clinical trials. Journal of Psychiatric Research 2011; 45(9): 1202-1207. [4]Tufts Center for Drug Development, New Drug Success Rates at Top 10 Pharma Companies: A 2006 Study in Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/7. Page 200; DiMasi, et al, Tufts Center for the Study of Drug Development, The price of innovation: new estimates of drug development costs. Journal of Health Economics, 22(2003) pp151-185. [5]Pharmaprojects Pharmapredict, Development Phase Lengths and Attrition Rates for Selected Therapeutic Categories in Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/7. Page 173. McKinsey/Lehman Brothers, The Fruits of Genomics. January 2001; BCG: A Revolution in R&D: The Impact of Genomics. June 2001.

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